# Study of intravenous tramadol versus rectal tramadol for postoperative analgesia after appendectomy

# Sandipbhai Jivanbhai Patel<sup>1,\*</sup>, Ajay Dyanoba Subhedar<sup>2</sup>

<sup>1</sup>Assistant Professor, Dept. of Anaesthesia, <sup>2</sup>Associate Professor, Dept. of Surgery, SBHGMC, Dhule, Maharashtra

#### \*Corresponding Author:

Email: sandip2027@yahoo.co.in

#### Abstract

**Introduction:** Tramadol is atypical opioid having central as well as peripheral analgesic action. It acts on opioid receptors as well as having effect on neuronal reuptake of nor epinephrine and serotonin. In this study, the effects of tramadol given by two different routes, intravenous and rectal, were compared in terms of analgesic efficacy and duration as well as its side effects in appendectomy patients.

**Material and Methods:** Forty patients of acute appendicitis undergone appendectomy under spinal anesthesia between age group of 20 to 50 years, of either sex having weight of 40 to 70 kg and ASA 1 or 2 physical status were included in the study to receive either Tramadol 100mg intravenously (Group A) or 100 mg rectal suppository (Group B) at the end of surgery. First onset of pain, VAS score, rescue analgesic requirement and side effects noted.

**Results:** Demographic parameters were comparable in both groups. Mean duration of first onset of pain in group B (417.5 $\pm$ 128.22min) was longer than group A (304 $\pm$ 86.16 min) and it was statistically significant (tailed significance value of 0.0010). Rescue analgesic requirement was significantly prolonged in group B than group A. Also incidence of postoperative vomiting was less in group B than group A (5% Vs 20%).

**Conclusion:** We conclude that rectal tramadol can be better alternative to intravenous tramadol for postoperative analgesia in appendectomy.

Keywords: Appendectomy, Analgesia, Tramadol, Intravenous, Rectal.

Date of Acceptance: 16th January, 2017

#### Date of Manuscript Receive: 27th October, 2016

## Introduction

Pain is a subjective manifestation of unpleasant, personal and nontransferable experience and includes both sensory-discriminative and motivational affective components. Surgical pain is produced by tissue injury involving physical and chemical body mechanisms. The Joint Commission Accreditation of Healthcare Organizations<sup>(1)</sup> has described pain as the fifth vital sign in 2001. Due to its importance, pain should be evaluated and recorded along with other vital record keeping. Surgery is important cause of acute pain. Acute appendicitis is a very common disease with prevalence of 8.6 and 6.6% among men and women respectivelly.<sup>(2,3,4)</sup> Generally 7% of total population undergoes appendectomy.<sup>(3)</sup> Something between 30 to 40% patients undergoing abdominal surgery suffer from moderate to severe pain.<sup>(5)</sup> Various parameters such as type of surgery, duration of surgery, type of anesthesia, mental and emotional status of patient etc. influence the severity of pain felt by patient.<sup>(6)</sup> For decreasing postoperative pain different methods and medicines are used. These include different opioid, non-steroidal anti inflammatory drugs (NSAID), local anesthetic infiltration, use of PCA (patient controlled analgesia) pumps, epidural technique and so on. Opioid and NSAID are cost effective and very commonly used. Systemic opioid use, can be associated with side effects such as nausea, vomiting, respiratory depression, constipation, itching, dizziness etc.<sup>(7,8)</sup> In addition

systemic NSAID can be associated with rash, analgesic nephropathy, exacerbation of peptic ulcer disease, bleeding etc. Tramadol is atypical opioid that have moderate affinity for mu receptor and weak kappa and delta opioid receptor affinity. In addition mu opioid agonist effect, tramadol enhances the function of spinal descending inhibitory pathway by inhibition of neuronal reuptake of nor epinephrine and serotonin as well as pre-synaptic stimulation of serotonin release. Tramadol is well tolerated by patients. Compared to morphine, tramadol has much less respiratory depression, cardiac depression, light headedness and sedative effect. Also addiction and abuse is much less with tramadol.<sup>(9,10,11)</sup> The only troublesome side effect of tramadol is nausea and vomiting. That can be prevented by antiemetic drugs.<sup>(12,13)</sup> Tramadol is available in all formulations i.e. oral, injectable (intramuscular, intravenous, intrathecal) and rectal. Tramadol used by different routes such as intravenous, intramuscular, rectal or local infiltration etc. have analgesic efficacy with different duration and variable incidence of side effects.<sup>(14,15,16,17)</sup> Some found local infiltration of tramadol and rectal tramadol having longer analgesic duration with less nausea and vomiting incidence. Intravenous tramadol is commonly used. However rectal route of tramadol is not much studied. With this background we have decided to compare intravenous tramadol 100mg versus rectal tramadol 100mg for postoperative analgesia in appendectomy patients with following aims and objectives:

- 1. **Primary aim and objective:** To study analgesic efficacy and duration with intravenous and rectal routes of drug administration.
- 2. Secondary aim and objective: To study incidence of side effects if any.

# Material and Methods

The study was prospective, randomized, comparative and hospital based. It was conducted on forty patients of either sex, presented with acute appendicitis and undergone emergency appendectomy by Mcburney's approach under spinal anesthesia after appropriate approval. Convenient sampling done between period of 15/03/16 to 15/10/16 and as many as patients (here 40 patients) presented with appendicitis as per inclusion criteria were studied in our hospital with their consent.

**Inclusion criteria:** 1) age group of 20 to 50 years 2) weight of 40 to 70 kg 3) American society of anesthesiologist's (ASA) 1 or 2 physical status. 4) patient with written informed valid consent.

**Exclusion criteria:** 1) pediatric and geriatric debilitated patients 2) patient having known drug allergy 3) patient with ASA status of 3 or more 4) patients found to have intra-abdominal collection on ultrasonography (suggestive of appendicular perforation).

With complete evaluation, investigations and written informed valid consent patients were randomly divided into two groups of 20 each as group A or group B by picking up random numbered chits labeled as either 'Intravenous' or 'Rectal'. Also preoperatively patients were explained about visual analogue scale (VAS), a 10 cm line with 0 cm equaling no pain and 10 cm worst pain ever felt.

After taking patient on operation table multipara monitor applied and baseline parameters noted. Intravenous line secured with 20 gauge intracath and infusion of ringer lactate started with injection ranitidine 50mg and injection metoclopramide 10 mg added to it. Spinal anesthesia given with 25 gauge spinal needle in L3-L4 interspace with 0.5% bupivacaine heavy 3 c.c. with desired level of T6. Appendectomy done by Mcburney's approach. At the end of surgery depending upon randomization 100 mg tramadol given intravenously to group A patients and 100 mg tramadol suppository inserted per rectally in group B patients for postoperative analgesia by anesthesia resident who picked up random numbered chit. Also he was not involved in any data collection. This was considered 0 hour. Both patient and data collecting anesthetist did not know the route of administration of tramadol. Post operatively time of first onset of pain noted. Also VAS score noted at 1, 2, 4, 6, 8, 10, 12 & 14 hour. At VAS score of 4 or more rescue analgesic had given with injection diclofenac 75 mg intramuscularly. Postoperatively side effects if any were noted. Incidence of nausea-vomiting and local rectal site burning or discomfort noted in all patients of both groups.

# Results

Data collected and statistical analysis done. Results were expressed as mean with standard deviation.

Statistical test – Statistical analysis done using IBM SPSS version 20.0 software (AppOnFly, Inc Online IBM SPSS started in 2005). T test applied and one tailed significance value calculated.

Demographic parameters like age, sex and weight were comparable in both groups (Table 1). In our trial with randomization sex ratio was comparable in both groups. 16 patients had ASA status of 1 and 4 had ASA status of 2 in each group. In group A out of 4 patients of ASA 2 two patients had controlled hypertension, one had controlled diabetes and one had mild anemia. In group B two patients had controlled hypertension, one had asthma history and one had borderline raised liver enzymes.

Parameters	Group A(IV tramadol) Mean±SD	Group B(Rectal tramadol) Mean±SD	1-tailed significance value
Age (Years)	29.95±8.8998	27.8±8.6304	0.2214
Weight (kg)	58.65±3.8835	58.3±4.9214	0.4020
Sex (M/F)	12/8	12/8	

Table 1: Demographic parameters

Mean duration of surgery was comparable in both groups (Table 2).

Table 2: Duration of surgery						
Parameters	Group A(IV tramadol)	Group B(Rectal	1-tailed			
	Mean±SD	tramadol) Mean±SD	significance value			
Duration of surgery (minute)	54.75±12.5105	50.5±12.9675	0.1490			

Tuble 5. This in industribus trainador Broup								
	1hr	2 hr	4hr	6hr	8hr	10hr	12hr	14hr
0	20	19	11	2	9	10	9	8
1	0	1	5	2	0	3	5	6
2	0	0	4	3	1	3	5	5
3	0	0	0	4	2	1	1	1
4 or more	0	0	0	9	8	3	0	0

#### Table 3: VAS in intravenous tramadol group

#### Table 4: VAS score in rectal tramadol group

		1hr	2hr	4hr	6hr	8hr	10hr	12hr	14hr
ſ	0	20	19	17	12	8	10	12	12
	1	0	1	2	3	2	3	1	1
ſ	2	0	0	1	2	1	2	2	2
ſ	3	0	0	0	2	1	2	3	2
	≥4	0	0	0	1	8	3	3	5

Table 5: Rescue analgesic requirement No. of patients with %

A t hour	Group A (IV tramadol)	Group B (Rectal tramadol)
1	0	0
2	0	0
4	0	0
6	9 (45%)	1 (5%)
8	8 (40%)	8 (40%)
10	3 (15%)	3 (15%)
12	0	2 (10%)
14	0	5 (25%)

Table 6: First onset of pain

Parameters		s	Group A(IV	Group B(Rectal	1-tailed		
			tramadol) Mean±SD	tramadol) Mean±SD	significance value		
Duration	of	first	304±86.1699	417.5±128.2216	0.001096		
pain(min.)							

#### Table 7: Postoperative nausea-vomiting and rectal site burning No. of patients with %

	Group A(IV tramadol)	Group B(Rectal tramadol)
PONV	4 (20%)	1 (5%)
Rectal site burning	0	0

## Discussion

Pain is an unpleasant sensory and emotional experience of varying intensity. It can be caused by actual or potential damage or described in such type of damage. Postoperative pain is important in causing psychological trauma to the patient. It leads to a restless and uncooperative patient. Meticulous management of postoperative pain is very important for early mobilization and discharge of patient as well as for good patient satisfaction. Opioid are commonly used in management of postoperative pain. Tramadol is atypical opioid being having action on opioid receptor as well as effect on nor epinephrine and serotonin pathways. It has fewer side effects as compared to morphine. It thus seems that tramadol may be suitable to treat postoperative pain. Use of same drug by different routes lead to alteration in onset, duration, efficacy and incidence of side effects. In per operative

period, considering NBM (nil by mouth) period oral route is not feasible and may cause gastric bloating, nausea or vomiting. Intramuscular route is painful. After intravenous administration of tramadol peak concentrations are reached rapidly. This has been associated with postoperative nausea and vomiting. This limits the use of tramadol as a postoperative analgesic, especially in day surgery.<sup>(18)</sup> Rectal suppository of tramadol may be an alternative in this situation. In our study we have compared intravenous versus rectal tramadol for postoperative analgesia in appendectomy patients. Patients when awake generally dislike rectal administration of drug. In our study we introduced tramadol suppository under effect of spinal anesthesia at the end of surgery, avoiding patient discomfort. A rectal dose of 1.5-2.0 mg/kg is therapeutic.<sup>(19)</sup> Therefore; we selected a dose of 100 mg in our study for suppository. Tramadol is rapidly

distributed after intravenous administration and the onset is fast with a distribution half-life in the initial phase of 6 minute.<sup>(20)</sup> After rectal administration, tramadol was detected from 5 minute up to 10 hour in dogs. After suppository, though absorption of the active ingredient was rapid, its metabolism quickly transformed the parent drug to high levels metabolites such as N-desmethyl-tramadol (M2) and N, Odidesmethyl-tramadol (M5).(21) The exact duration of analgesia after tramadol suppository is to be studied in brief yet. In our study the mean duration of analgesia i.e. mean duration of first onset of pain in rectal tramadol group was longer i.e. 417.5±128.22 minute as compared to 307±86.16 minute in intravenous tramadol group (Table 6) which was statistically significant (tailed significance value of 0.0010). We studied VAS score in both groups (Table 3 & 4) and gave rescue analgesic at score of 4 or more. In our study, it was shown that 45% of the patients needed first rescue analgesic at 6 hour in intravenous tramadol group (group A) whereas only 5% of the patients in rectal tramadol group (group B) needed it, which was a significantly lower proportion. By the end of 8 hours and 10 hrs total of 85% and all 100% patients received rescue analgesic in intravenous tramadol group respectively. By the end of 8 hours and 10 hours total of only 45% and 65% patients in suppository group received rescue analgesia respectively. Remaining 10% and 25% patients in suppository group needed rescue analgesia at 12 and 14 hours respectively (Table 5). Thus the duration of analgesia was prolonged with Group B, which was observed by time for first onset of pain, time for need of rescue analgesic and percentage of patients who required it in both groups. The maximal plasma concentrations of tramadol and its metabolite (O-demethylatedtramadol) were 200 (60) and 35 (15) ng/ml at 2.4 (1.0) and 3.9 (1.1) hour after rectal administration.<sup>(19)</sup> After the 2 mg/kg dose of tramadol, the time interval of therapeutic concentration would be 8.6 (1.1) hour and it could be correlated with the duration of analgesia.<sup>(19)</sup> M1 contributes to the analgesic effect of rectally administered tramadol, one- to fourtimes higher than the parent compound. The mean absolute bioavailability after rectal administration is 78%.<sup>(22)</sup> Tramadol is having nausea and vomiting as troublesome side effect. Different authors studied this side effect by using tramadol by different route. In our study 1 patient (5%) in group B had single episode of vomiting postoperatively as against 4 patients (20%) in group A and all were responded to ondansetron injection (Table 7). No one patient from both groups was complaining of local rectal site burning. Our all previous above results are comparable to studies.(15,16,17,24) M. Lotfalizade et al<sup>(15)</sup> studied diclofenac suppository against intravenous tramadol injection and combination of these two for analgesia in caesarean section and found mean analgesic duration of 134.7 minutes in intravenous tramadol group. Hina N.

Gadani et al<sup>(16)</sup> studied analgesic efficacy of rectal tramadol against intravenous tramadol for adult tonsillectomy. They found significantly prolonged duration of analgesia in rectal group as against intravenous tramadol group (504±146.96 min vs. 426±80.36 min). Also they found 15% incidence of postoperative nausea-vomiting (PONV) in intravenous tramadol group as against 5% in rectal suppository group. Dr. Joshi V.S. et al<sup>(17)</sup> studied rectal suppository of tramadol and diclofenac in caesarean section. They found 3.33% incidence of PONV in rectal tramadol group. V. Khazin et al<sup>(23)</sup> studied postoperative analgesia with rectal tramadol and indomethacin for diagnostic curettage and early termination of pregnancy. They found rectal tramadol provides superior postoperative analgesia with minimal adverse effects.

Thus various oral, rectal and parenteral formulations of tramadol are available. The rectal route may represent a practical alternative. Limitations of our study are that we have used convenient sampling method. Also we have studied postoperative analgesia only for 14 hours. Elaboration of postoperative nauseavomiting may require large sample size. Further prospective studies with large sample size are warranted.

# Conclusion

Duration of analgesia is prolonged with rectal route of tramadol. It also adds to increase patient comfort by minimizing postoperative nausea-vomiting. Thus we conclude that rectal tramadol suppository can be better alternative to intravenous tramadol with longer postoperative analgesia in appendectomy patients with minimal side effects.

## References

- Joint Commission on Accreditation of Healthcare Organizations (JCAHO). National Pharmaceutical Council (NPC). Pain: current understanding of assessment, management, and treatments. Reston: NPC; 2001.
- 2. Korner H, Sondenaa K, Soreide JA, Andersen E, Nysted A, Lende TH, et al. Incidence of acute nonperforated and perforated appendicitis: age-specific and sex-specific analysis. World J Surg. 1997;21(3):313-7.
- 3. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 1990;132(5):910-25.
- Korner H, Soreide JA, Pedersen EJ, Bru T, Sondenaa K, Vatten L. Stability in incidence of acute appendicitis. A population-based longitudinal study. Dig Surg. 2001;18(1):61-6.
- 5. Almeida OJ, Val-Gallas JM, Rizk B. Appendectomy under local anesthesia following conscious pain mapping with microlaparoscopy. Hum Reprod. 1998;13(3):588-90.
- Lowenstein L, Zimmer EZ, Deutsch M, Paz Y, Yaniv D, Jakobi P. Preoperative analgesia with local lidocaine infiltration for abdominal hysterectomy pain management. Eur J Obstet Gynecol Reprod Biol. 2008;136(2):239-42.

- 7. Cheever KH. Pain, analgesic use, and morbidity in appendectomy patients. Clin Nurs Res. 1999;8(3):267-82.
- Radbruch L, Grond S, Lehmann KA. A risk-benefit assessment of tramadol in the management of pain. Drug Saf. 1996;15(1):8-29.
- Robert K. Stoelting, Simon C. Hillier. Pharmacology and physiology in anesthetic practice, fourth edition. Opioid agonists and antagonists, page 87-126.
- Lee CR, Mc Tavish D, Sorkin EM. Tramadol: A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in acute and chronic pain states. Drugs. 1993;46:313–40.
- Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol. An atypical opioid analgesic. J Pharmacol Exp Ther. 1992;260:275–85.
- Pang WW, Wu HS, Lin CH, Chang DP, Huang MH. Metoclopramide decreases emesis but increases sedation in tramadol patient-controlled analgesia. Can J Anaesth. 2002;49(10):1029-33.
- Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. Drugs. 2000;60(1):139-76.
- Altunkaya H, Ozer Y, Kargi E, Ozkocak I, Hosnuter M, Demirel CB, et al. The postoperative analgesic effect of tramadol when used as subcutaneous local anesthetic. Anesth Analg. 2004;99(5):1461-4.
- 15. M. Lotfalizade, N. Zirak et al. Comparison of effects of diclofenac suppository and tramadol injection and combination of these two drugs on pain after spinal anesthesia for cesarean. Iranian Journal of Obstetrics, Gynecology and Infertility. Dec. 2015;17(131):1-5.
- Hina N. Gadani, Virendra Pratap Chaudhary. Comparative study of the analgesic efficacy of rectal tramadol versus intravenous tramadol for adult tonsillectomy. Anesth Essays Res. 2010 July-Dec;4(2):102-105.
- 17. Dr. Joshi V.S. et al. Comparative study of analgesic efficacy of rectal suppository of tramadol versus diclofenac in suppressing postoperative pain after Cesarean section. International J. of Healthcare and Biomedical Research. January 2013, Volume: 2, P 32-37.
- Petron D, Kamin M, Olson W. Slowing the titration rate of tramadol HCL reduces the incidence of discontinuation due to nausea and /or vomiting. A double blindrandomized trial. J Clin Pharm Ther. 1999;24:115–23.
- Zwaveling J, Bubbers S, van Meurs AH, Schoemaker RC, van Heel IR, Vermeij P, et al. Pharmacokinetics of rectal tramadol in postoperative pediatric patients. Br J Anaesth. 2004;93:224–7.
- Eggars KA, Power I. Tramadol. Br J Anaesth. 1995;74:247–9.
- Giorgi M, Del Carlo S, Saccomanni G, Lebkowska-Wieruszewska B, Kowalski CJ. Pharmacokinetics of tramadol and its major metabolites following rectal and intravenous administration in dogs. N Z Vet J. 2009;57:146–52.
- 22. Dayer P, Desmeuls J, Collart L. Pharmacology of tramadol. Drugs. 1997;53:18–24.
- V. Khazin, S. Weitzman, E. Rozenzvit-Podles, T. Ezri, A. Debby, A. Golan, S. Everon. Postoperative analgesia with tramadol and indomethacin for diagnostic curettage and early termination of pregnancy. International Journal of Obstetric Anesthesia, (2011) 20,236-239.